REMARKS

The Office Action of June 8, 2010 constitutes a non-final rejection of the claims. The Office Action and the references relied upon therein have been carefully reviewed. Reconsideration and allowance of the claims are requested in view of the foregoing amendments and the following remarks.

I. Claim Status and Amendments

Claims 1, 3, 5, 7, 8, and 54-57 remain pending in this application and stand rejected. No claims have been allowed.

By way of the present amendment, claim 57 has been amended to specify that the claimed method produces $O1^+$ and/or $O4^+$ oligodendrocytes with large myelin membranes and more aborization, as compared to control NS cells not grown in said culture medium. Support can be found throughout the general disclosure. See for instance, Examples 6-7 at paragraphs [0142 to 0145] of the corresponding publication (i.e., US Patent application publication no. 20070237748).

No new matter has been added.

Claims 1, 3, 5, 7, 8, and 54-60 are pending upon entry of this amendment, and these claims define patentable subject matter warranting their allowance for the reasons discussed herein.

II. Indefiniteness Rejections

Claims 54 and 55 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite, for the reasons set forth in item 4 on pages 3-5 of the Office Action. This rejection is respectfully traversed.

As to the rejection of claim 54, the Examiner, on page 3, argues that "the culture medium itself contains a lot of growth agents (more than one) to maintain and promote cell survival" in addition to the gp130 activators recited in claim 54. Specifically, the examiner argues that the culture medium for NS cells described in the specification contains DMEM/F12, heparin, FGF-2, insulin, transferring, putrescine, selenite, progesterone (pages 14 & 29 of the disclosure) and the differentiation medium contains DMEM/F12 with insulin, transferrin, putrescine, selenite, progesterone (page 29), and these agents are the growth or differentiation agents, and thus, the culture medium itself recited in claim 54 has already contained more than one growth or differentiation agents. The Examiner argues that this disclosure conflicts with the claims. The Examiner concludes that since the culture medium itself recited in claim 54 already contains more than one growth or differentiation agent, then it is inconsistent for the claim to specify that the one or more

gp130 activators is the only growth or differentiation agent present in the culture medium.

Applicants respectfully disagree for the reasons set forth in the response filed March 16, 2010, which arguments are reiterated herein by reference, and for the following reasons.

The noted claim language clearly requires that the gp130 activator is the only growth or differentiation agent present in the culture medium. It should be further noted that nothing in the claims requires the culture medium to always contain the other factors noted by the Examiner. The claims in question broadly encompass an embodiment in which the culture medium does not have the other growth factors noted by the Examiner in it, but it only has the gp130 activator as the growth factor. The Examiner has provided no basis as to why Applicants should not be entitled to claim this embodiment.

Further, the specification clearly discloses this embodiment. See for instance, the last paragraph on page 14, wherein it is described that the gp130 activator is added to the NS cells to promote formation of oligodendrocyte progenitors "either alone or together with other growth or differentiation agents such as retinoic acid, EGF, PDGF etc."

This disclosure is clear. It is not ambiguous, nor does conflict with the claims.

Yet, the Examiner repeatedly argues that the culture medium must always contain the other noted factors. However, this position amounts to improperly reading limitations from the specification into the claims by taking the position that the culture medium in the claims must always require the other noted elements. Again, this is improper, because the claims do not require this for the reasons noted above. Pursuant to US practice as enumerated at MPEP 2111.01, "[t]hough understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim." Thus, it is improper for the Examiner in this case to import claim limitations from the specification.

For these reasons, the indefiniteness rejection of claim 54 should be withdrawn.

On page 4, the Examiner has maintained the indefiniteness rejection of claim 57 for the language "large and highly branched $O1^+$ and/or $O4^+$ oligodendrocytes exhibiting large myelin membranes." The Examiner argues that the terms "large" and "highly branched" are relative and indefinite. Applicants respectfully disagree. Nonetheless, Applicants

have amended claim 57 in a manner believed to obviate this rejection.

Specifically, claim 57 has been amended to clarify that the claimed method produces $O1^+$ and/or $O4^+$ oligodendrocytes with large myelin membranes and more aborization, as compared to control NS cells not grown in said culture medium. Support can be found in the disclosure, for and at Examples 6-7 at paragraphs [0142 to 0145] of the corresponding publication (i.e., US Patent application publication no. 20070237748) of the application. These examples demonstrate that the present invention, as claimed, results in oligodendrocytes with more aborization (i.e., highly branched) and they grew to a much larger size than in control samples (without treatment by gp130 activators). The claims have been amended to reflect this.

Further, it should be noted that the controls discussed in the examples provide a standard for determining what is large as compared to normal, such that the skilled artisan would clearly understand what is meant by large myelin membranes with more aborization, as claimed. As such, the skilled artisan would clearly understand the terms "large" and "more aborization" with respect to $O1^+$ and/or $O4^+$ oligodendrocytes as compared to oligodendrocytes of normal

size. Thus, the claim, as amended, is thus clear and definite.

For these reasons, the indefiniteness rejection of claim 57 should be withdrawn.

III. Obviousness Rejections

Claims 1, 3, 5, 7, 8, and 54-60 have been newly rejected under 35 U.S.C. 103(a) as being unpatentable over Gearhart et al. (US 6,562,619) in view of Zhang et al. (Nat. Biotechnol., 2001, Dec, 1129-1133) as evidenced by Baumann et al. (Physol. Rev. 2001, 81:871-927) and Billon (J. Cell Sci., 2002, 115:3657-36665) for the reasons set forth on pages 6-11 of the Action.

This rejection is respectfully traversed.

First, the instant claims, as represented by main claim 1, are directed to a method for generating $O1^+$ and/or $O4^+$ oligodendrocytes, said method comprising growing neurosphere (NS) cells in a culture medium that promotes differentiation of NS cells into $O1^+$ and/or $O4^+$ oligodendrocytes, by using gp130 activators selected from the group consisting of CNTF, oncostatin-M (OSM), IL-6, IL6R/IL6 chimera and IL-11 in the culture medium, and wherein said culture medium specifically enhances differentiation into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$

oligodendrocytes. As such, the claims of the present application clearly require that the starting material is neurospheres. However, the primary reference of Gearhart clearly fails to disclose the use of neurospheres. Indeed, the word neurospheres nowhere appears in the disclosure of Gearhart. The Examiner even acknowledges that Gearhart fails to disclose neurospheres derived from embryoid bodies, as the starting materials, as required in the claims.

Further, the disclosure in Gearhart relates to a different method than the claimed invention. In particular, Gearhart relates to a method for producing a cell population of embryoid bodies (see claims 1 and 8), and not to a method for generating $O1^+$ and/or $O4^+$ oligodendrocytes. As discussed in the last response, a review of the specification and the scientific literature makes it clear that embryoid bodies, as disclosed in Gearhart, are not the same as neurospheres. In this regard, embryoid bodies are aggregates of cells derived from embryonic stem cells. Embryoid bodies comprise a large variety of differentiated cell types; they first form a ball of cell and then take on a more complex appearance with different layers of structure containing different cells. This is supported by the instant application. See for instance, the bottom page 11, wherein it is disclosed that embryoid bodies include primitive endoderm and ectoderm layers. See also the

discussion in Carpenter (previously cited) (at page 11 lines 31-32), which describes the embryoid bodies as a heterogeneous cell population.

By contrast, neurospheres are a free floating structures generated by neural stem cells. They do not include the primitive endoderm and ectoderm layers of embryoid bodies. Neurospheres are more homogenous in structure and cell type. Thus, it should be clear that neurospheres are not the same as embryoid bodies, even though they can be obtained from embryoid bodies. Again, neurospheres are more homogenous in structure and cell type, since they comprise neural stem cells, as opposed to embryoid bodies that contain numerous cell types.

Based on the above, it is clear that the Gearhart fails to disclose or suggest the use of neurospheres; and the method of Gearhart is directed to producing embryoid bodies, and not to a method for generating $O1^+$ and/or $O4^+$ oligodendrocytes.

Despite such, the Examiner argues that in the method of Gearhart, the cells go through 1-3 passages of re-dissociation, resuspension and repassages from embryoid bodies (i.e. originally derived from embryonic stem cells), and this would give rise to neurospheres because the cells cultured in the method of Gearhart are re-suspended and passaged and cultured in the same manner as the cells in Zhang (2001) and

as in instant specification. The Examiner further states that the cells derived from embryoid bodies as taught by Gearhart would have similar properties as neurospheres as recited in claim 1. Applicants respectfully disagree.

As discussed above, Gearhart is directed to a method of producing embryoid bodies, and not to a method for generating $O1^+$ and/or $O4^+$ oligodendrocytes. Also, as discussed above, the embryoid bodies disclosed in Gearhart are significantly different from neurospheres, so much so, that they are not suggestive of each other.

Further, the present claims specify enhancing differentiation into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. Gearhart does not disclose this. Gearhart fails to disclose a method using a culture medium that promotes the preferential differentiation into oligodendrocytes as claimed. Gearhart only teaches generalized differentiation and does not teach how to obtain preferential differentiation into oligodendrocytes. Gearhart does not disclose specific differentiation into oligodendrocytes, because the methods in the prior art result in a mixture of cells. Thus, contrary to the Examiner's position, the methods in Gearhart and the cells

produced there from are different from those in the instant claims.

Given that Gearhart does not disclose or suggest selecting neurospheres from the large variety of cell types present in embryoid bodies, it follows then that neurospheres are not necessarily present in the cells disclosed and used in the methodology of Gearhart.

In fact, at the top of page 9 of the Office Action, the Examiner acknowledges that the primary reference of Gearhart fails to disclose expression of $O1^+$ and $O4^+$ markers on differentiated oligodendrocytes.

For these reasons, the claims are believed to be novel and patentable over Gearhart.

Zhang (2001), even if combined with Baumann and Billon, fails to remedy the deficiencies in Gearhart.

Zhang (2001) is relied upon for allegedly disclosing the use of neurospheres. On page 8 of the Office Action, the Examiner argues that in view of the teaching of Zhang (2001), human derived-ES cells can form embryoid bodies and neurospheres in the culture of human ES cells in the presence of FGF-2 as evidenced by Billon. The Examiner also relies on Zhang (2001) as allegedly disclosing that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into 04+,01+ and GFAP+ neural

precursor cells (see p. 1129-1130, in particular). At the bottom of page 9, the Examiner states that neurospheres can be derived from embryoid bodies from cultured human ES as taught by Zhang (2001).

Applicants respectfully submit that Zhang (2001) in no way suggests the claimed method, even if combined with Gearhart, Baumann and Billon. In this regard, Zhang (2001) is discussed in the background section of the instant application at paragraph [0004], wherein it is disclosed that:

> Human ES cell lines derived EBs also form neural tube like rosettes expandable as floating neurospheres that can be transplanted in vivo or plated on polycationic substrates to differentiate into neurons, astrocytes and oligodendrocytes, the latter developing particularly after treatment with PDGF-AA and T3 (Reubinoff et al. 2001; Zhang et al. 2001).

Also, at paragraph [0050] of the instant application, the following is disclosed:

> The use of ES cells derived transplants has many advantages over the use of fetal or adult brain cells. The ES cells have high potential for expansion in vitro, can be ascertained to be pathogen-free and histocompatibility could be achieved by maintaining banks of ES cell lines (as done for bone marrow transplantation) or by cloning (i.e. producing ES cells from blastocysts produced by nuclear transfer from one of the patient's own cell) (Lanza et al. 1999). Experimental transplantation to animals has been successfully achieved with neurospheres derived from murine ES

> cells (Brustle et al. 1999; Liu et al. 2000) and from human ES cells (Reubinoff et al. 2001; Zhang et al. 2001). This approach could be greatly improved by having a method to promote the differentiation of ES cells toward specific cell lineages, such as myelinating oligodendrocytes. [Emphasis added.]

As noted in these paragraphs, the approach referred to in Zhang (2001) does not disclose or suggest steps for the differentiation of ES cells toward specific cell lineages, such as myelinating oligodendrocytes. The present invention is an improvement over the method in Zhang (2001).

Yet, at the bottom of page 3 of the Office Action, the Examiner contends that there would be motivation to modify the references to arrive at the claims, because neurospheres can be derived from embryoid bodies from cultured human ES as taught by Zhang (2001) and the cells expanded and re-suspended from embryoid bodies in the presence of a gp130 activator, such as CNTF, OSM, LIF, IL-6 or IL-11, can be differentiated into O1+ and/or O4+ oligodendrocytes as taught by Gearhart.

Applicants respectfully disagree. Contrary to the Examiner's position, Zhang (2001) does not provide motivation to modify the method of Gearhart to solely use neurospheres. There is no rationale in the references or in the rejection itself urging the skilled artisan to use the neurospheres disclosed in Zhang (2001) in a method, such as that of

Gearhart, to generate O1+ and/or O4+ oligodendrocytes in the presence of a gp130 activator, such as CNTF, OSM, LIF, IL-6 or IL-11. Why would they do so? Again, the method in Gearhart is for producing embryoid bodies, which are a mixture of cells, and not for a method of utilizing neurospheres. There is no suggestion in the references to remove the extra cells from the mixture of cells in the embryoid bodies disclosed in Gearhart. Also, as acknowledged by the Examiner, Gearhart does not disclose a method for differentiation of cells, let alone neurospheres, into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes.

In addition, Applicants direct the Examiner's attention to Example 5 on pages 35-36 of the instant application. Example 5 investigates IL6RIL6 enhancement of oligodendrocyte lineage-specific gene expression. See specifically, page 35, line 31 to page 36, line 5. When embryoid bodies were treated with IL6RIL6, it resulted in little to no expression, as shown in Figure 2, lines 1-2. By contrast, when neurospheres were treated with IL6RIL6, it resulted in marked increase in expression. As stated at page 36, lines 9-11, "[t]hese gene expression profiles support the conclusion that gp130 activator exerts enhancing effects on

early phases of cell differentiation along the oligodendrocyte lineage (as denoted by Sox-10 and Olig-1 expression), as well as on them maturation toward myelinating MBP-expression oligodendrocytes."

This is clear evidence that the gp130 activator does not exert the same effect on embryoid bodies as it does on neurospheres. It follows then that the method in Gearhart, which produces embryoid bodies, would not produce the same result, as the claimed method, which utilizes neurospheres as the starting material. This, in turn, is evidence that the method for producing embryoid bodies of Gearhart does not result in enhancing differentiation into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes, because as shown in Example 5, embryoid bodies do not result in such preferential enhancement when treated with a gp130 activator. Again, the evidence in Example 5 further demonstrates that embryoid bodies are not neurospheres and *vice versa*. As such, there is no motivation to use neurospheres in the method of Gearhart with a reasonable expectation of success.

In fact, it should be noted that nowhere does Gearhart disclose the use of a culture medium in a method to specifically enhance differentiation to cause the NS cells to

differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. Instead, Gearhart relates to differentiation into a mixture of neuronal cells in general.

In view of the above, the combination of Gearhart and Zhang (2001) fails to disclose or suggest each and every element of the claims.

The remaining references of Bauman and Billon do nothing to resolve the deficiencies of Gearhart and Zhang (2001). Billon relates to a study on timing of oligodendrocyte development from genetically engineered-selectable mouse ES cells. Billon says nothing to suggest using neurospheres in the claimed method. Similarly, Bauman also says nothing to suggest using neurospheres in the claimed method.

For these reasons, it is respectfully submitted that no combination of Gearhart in view of Zhang (2001), as evidenced by Baumann and Billon, would disclose or suggest each and every element of the claims. Withdrawal of the rejection is respectfully requested.

IV. Conclusion

Having addressed all the outstanding issues, this paper is believed to be fully responsive to the Office Action. It is respectfully submitted that the claims are in condition for allowance and favorable action thereon is requested.

In the event that the Examiner disagrees and maintains one or more of the rejections, then kindly contact the undersigned attorney at the telephone number below to discuss comments or proposals for expediting prosecution.

Respectfully submitted,

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